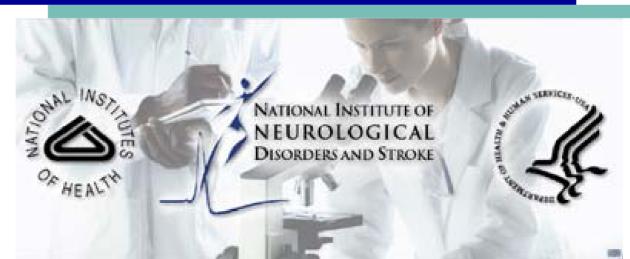
The SMA Project: A New Approach to Therapy Development at NIH

Jill Heemskerk, Ph.D.

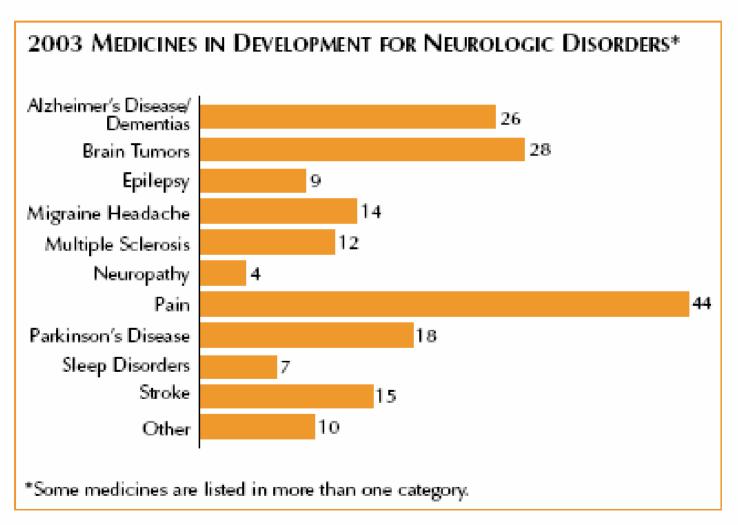
National Institute of Neurological Disorders and Stroke, NIH

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Industry Neurotherapeutics: 19 Disorders



450 NINDS Disorders

Absence of the Sentum Pellucidum Acquired Epileptiform Aphasia Acute Disseminated Encephalomyelitis ADHD Adrenoleukodystrophy Agenesis of the Corpus Callosum Agnosia Aicardi Syndrome AIDS - Neurological Complications Alexander Disease Alpers' Disease Alternating Hemiplegia Alzheimer's Disease Amyotrophic Lateral Sclerosis Aneurysm Angelman Syndrome Angiomatosis Aphasia Arteriovenous Malformation Asperger Syndrome Atavia Ataxia Telangiectasia Ataxias and Cerebellar/Spinocerebella Degeneration Attention Deficit-Hyperactivity Autism Autonomic Dysfunction Back Pain Barth Syndrome Batten Disease Behcet's Disease Benign Essential Blepharospasm Benign Focal Amyotrophy Benign Intracranial Hypertension Bernhardt-Roth Syndrome Binswanger's Disease Bloch-Sulzberger Syndrome Brachial Plevus Birth Injuries Bradbury-Eggleston Syndrome Brain and Spinal Tumors Brain Aneurysm Brain Injury Brown-Sequard Syndrome Bulhospinal Muscular Atrophy Carpal Tunnel Syndrome Cavernomas Cavernous Angioma Cavernous Malformation Central Cervical Cord Syndrome Central Cord Syndrome Central Pain Syndrome Cephalic Disorders Cerebellar Degeneration Cerebellar Hypoplasia Cerebral Aneurysm Cerebral Arteriosclerosis Cerebral Atrophy Cerebral Beriberi Cerebral Paley Cerebro-Oculo-Facio-Skeleta Syndrome Charcot-Marie-Tooth Disease Chiari Malformation Choreoacanthocytosis Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Chronic Orthostatic Intolerance Chronic Pain Cockayne Syndrome Type II Coffin Lowry Syndrome COES Coma and Persistent Vegetative Complex Regional Pain Syndrome Congenital Facial Diplegia Congenital Myasthenia Congenital Myonathy Congenital Vascular Cavernous Malformations Corticobasal Degeneration Cranial Arteritis Creutzfeldt-Jakob Disease Cumulative Trauma Disorders Cushing's Syndrome Cytomegalic Inclusion Body Disease (CIRD) Cytomegalovirus Infection Dancing Eyes-Dancing Fee Syndrome Dandy-Walker Syndrome Dawson Disease De Morsier's Syndrome Deen Brain Stimulation to Parkinson's Disease Dejerine-Klumpke Palsy Dementia - Subcortical Dementia With Lewy Bodies Dentate Cerebellar Ataxia Dentatorubral Atrophy Dermatomy ositi: Developmental Dyspraxia Diabetic Neuropathy Diffuse Sclerosis Dysautonomia Dysgraphia Dyslexia Dysphagia Dyspraxia Dyssynergia Cerebellaris Myoclonica Dyssynergia Cerebellaris Progressiva Dystonias Farly Infantile Enilentic Empty Sella Syndrome Encephalitis Lethargica Encenhaloceles Encephalopathy Encephalotrigeminal Angiomatosis Epilepsy Erb-Duchenne and Deierine-Klumpke Palsies Erb's Palsy Fabry's Disease Fahr's Syndrome Fainting Familial Dysautonomia Familial Hemangioma Familial Idiopathic Basal Ganglia Calcification Familial Periodic Paralyses Febrile Seizures Fisher Syndrome Floppy Infant Syndrome Friedreich's Ataxia Gaucher's Disease Gerstmann's Syndrome Gerstmann-Straussler-Scheinker Giant Cell Arteritis Giant Cell Inclusion Disease

Globoid Cell Leukodystrophy Glossopharyngeal Neuralgia Guillain-Barre Syndrome Hallervorden-Spatz Disease Head Injury Headache Hemicrania Continua Hemifacial Spasm Hemiplegia Alterans Hereditary Spastic Paraplegia Heredopathia Atactica Polyneuritiformis Hernes Zoster Herpes Zoster Oticus Hirayama Syndrome HTLV-1 Associated Myelopathy Huntington's Disease Hydranencephaly Hydrocophalue Hydrocephalus - Normal Pressure Hydromyelia Hypercortisolism Hypersomnia Hypertonia Hypotonia - Infantile Hypoxia Immune-Mediated Encephalomyelitis Inclusion Body Myositis Incontinentia Pigmenti Infantile Phytanic Acid Storage Disease Infantile Refsum Disease Infantile Spasms Inflammatory Myopathy Intestinal Lipodystrophy Intracranial Cysts Intracranial Hypertension Kearns-Sayre Syndrome Kennedy's Disease Kinshoume syndrome Kleine-Levin Syndrome Klippel-Feil Syndrome Klippel-Trenaunay Syndrome (KTS) Klüver-Bucy Syndrome Korsakoff's Amnesic Syndrome Kugelberg-Welander Disease Kuru Lambert-Eaton Myasthenic Syndrome Landau-Kleffner Syndrome Lateral Femoral Cutaneous Nerve Entrapment Lateral Medullary Syndrome Learning Disabilit Leigh's Disease Lennox-Gastaut Syndrome Lesch-Nyhan Syndrome Leukodystrophy Levine-Critchley Syndrome Lewy Body Dementia Lipid Storage Diseases Lissencephaly Locked In Syndrome Lou Gehrig's Disease Lupus - Neurological Seguelae Complications Machado-Joseph Disease Macrencephaly Megalencephaly Melkersson-Rosenthal Syndrome

Meningitis

Menkes Disease

Meralgia Paresthetica

Metachromatic Leukodystrophy Microcephaly Migraine Miller Fisher Syndrome Mini-Strokes Mitochondrial Myopathies Mobius Syndrome Monomelic Amvotrophy Motor Neuron Diseases Moyamoya Disease Mucolinidoses Mucopolysaccharidoses Multifocal Motor Neuropathy Multi-Infarct Dementia Multiple System Atrophy Multiple System Atrophy with Orthostatic Hypotension Muscular Dystrophy Myasthenia - Congenital Myaethonia Gravie Myelinoclastic Diffuse Sclerosis Mynclonic Encenhalonathy of Myoclonus Myopathy Myopathy - Congenita Myopathy - Thyrotoxic Myotonia Myotonia Congenita Narcolepsy Neuroacanthocytosis Neurodegeneration with Brain Iron Accumulation Neurofibro matosis Neuroleptic Malignant Syndrome Neurological Complications of AIDS Neurological Complications Of Lyme Neurological Manifestations of Pompe Disease Neurological Sequelae Of Lupus Neuromyelitis Ontica Neuronal Ceroid Lipofuscinosis Neuronal Migration Disorders Neuropathy - Hereditary Neurotoxicity Nevus Cavernosus Niemann-Pick Disease Normal Pressure Hydrocephalus Occipital Neuralgia
Occult Spinal Dysraphism Sequence Ohtahara Syndrome Olivopontocerebellar Atrophy Onsocionus Myocionus O'Sullivan-McLeod Syndrome Overuse Syndrome Pain - Chronic Pantothenate Kinase-Associated Neurodegeneration Paraneoplastic Syndromes Parkinson's Disease Parmyotonia Congenita Paroxysmal Choreoathetosis Paroxysmal Hemicrania Parry-Romberg Pelizaeus-Merzhacher Disease Perineural Cysts

Pinched Nerve Piriformis Syndrome Pituitary Tumors Polymyositis Pompe Disease Porencephaly Postherpetic Neuralgia Postinfectious Encephalomyelitis Post-Polio Syndrome Postural Hypotension Postural Orthostatic Tachycardia Syndrome Postural achycardia Syndrome Primary Dentatum Atrophy Primary Lateral Sclerosis Prion Diseases Progressive Hemifacial Atrophy Progressive Locomotor Ataxia Progressive Multifocal Leukoencephalopathy Progressive Sclerosing Poliodystrophy Progressive Supranuclear Palsy Pseudotumor Cerebri Ramsay Hunt Syndrome Ramsay Hunt Syndrome I (formerly Ramsav Hunt Syndrome II Rasmussen's Encephalitis Reflex Sympathetic Dystrophy Syndrome Refsum Disease Referm Disease - Infantile Repetitive Motion Disorders Renetitive Stress Injuries Restless Legs Syndror Retrovirus-Associated Myelopathy Rett Syndrome Reve's Syndrome Riley-Day Syndrome Sacral Nerve Root Cysts Saint Vitus Dance Sandhoff Disease Schizencephaly Seizure Disorder Septo-Optic Dysplasia Shaken Baby Syndrome Shy-Drager Syndrome Sleep Apnea Soto's Syndrome Spinal Cord Infarction Spinal Cord Injury Spinal Cord Tumors Spinal Muscular Atrophy Spinocerebellar Atrophy Spinocerebellar Degeneration Steele-Richardson-Olszewski Syndrome Striatonigral Degeneration Stroke Sturge-Weber Syndrome Subacute Sclerosing Panencephalitis Subcortical Arteriosclerotic SUNCT Headache Swallowing Disorders Sydenham Chorea Syncope Syphilitic Spinal Sclerosis

Syringohydromyelia

Syringomyelia Systemic Lupus Erythematosus

Tardive Dyskinesia Tarlov Cysts
Tay-Sachs Disease Temporal Arteritis Tethered Spinal Cord Syndrome Thomson Disease Thoracic Outlet Syndrome Thyrotoxic Myonathy Tic Douloureux Todd's Paralysis Tourette Syndrome Transient Ischemic Attack Transmissible Spongiform Transverse Myelitis Traumatic Brain Injury Tremor Trigeminal Neuralgia Tropical Spastic Paraparesis Tuberous Sclerosis Vasculitis including Temporal Von Economo's Disease Von Hippel-Lindau Disease (VHL) Von Recklinghausen's Disease Wallenberg's Syndrome Werdnig-Hoffman Diseas Wernicke-Korsakoff Syndrome West Syndrome Whiplash Whipple's Disease Williams Syndrome Wilson's Disease X-Linked Spinal and Bulbar Muscular Atrophy Zellweger Syndrom

Peripheral Neuropathy

Periventricular Leukomalacia

Phytanic Acid Storage Disease

Pervasive Developmental Disorders

Persistent Vegetative State

The SMA Project

- What is it?
 - An \$22MM NINDS therapeutics program for Spinal Muscular Atrophy (SMA)
 - A pilot for other rare diseases
- Goal:
 - New drugs for testing in SMA patients





Rationale for SMA as a Pilot

◆ Defined cause = loss of SMN1 gene

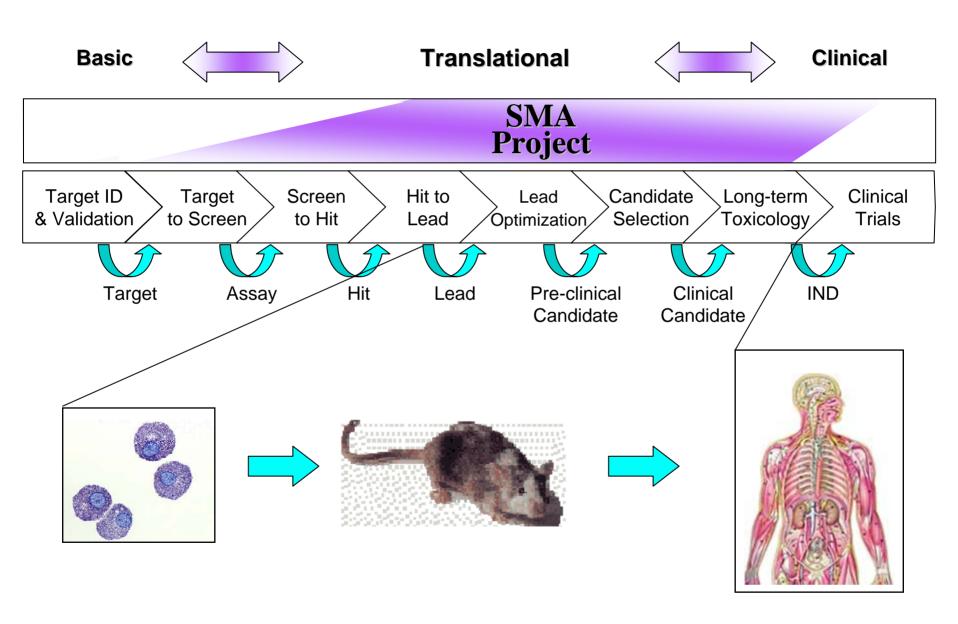
 Defined strategy for treatment = SMN2: identical protein, low expression

Compounds that increase SMN2 expression





SMA Project Focus



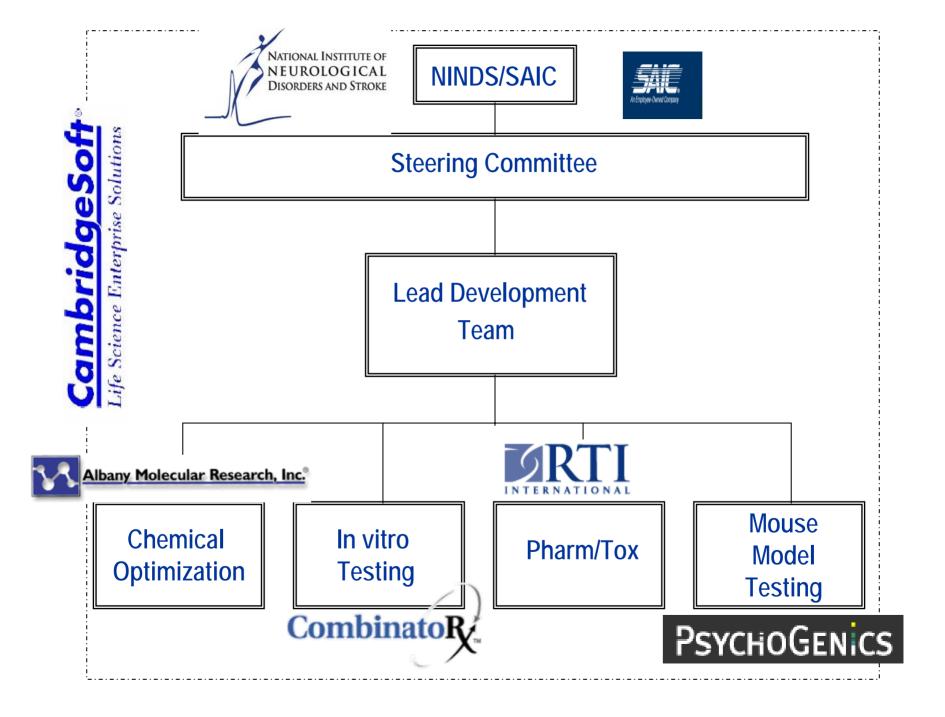
Scientific Steering Committee

- Chair: Robert Pacifici, CHDI, Inc. (formerly Lilly)
- John M. McCall, PharMac LLC (formerly Pfizer)
- Graham Johnson, Rib-X Pharmaceuticals (formerly BMS)
- Edward Hall, University of Kentucky (formerly Pharmacia & Upjohn)
- Perry Molinoff, Univ. of Pennsylvania (formerly BMS)
- Allan Tobin, High Q Foundation
- Howard Federoff, Rochester University
- Diana Escolar, Children's Hospital
- Richard Ransohoff, Cleveland Clinic
- Kurt Fischbeck, NINDS Intramural (ex officio)
- Tan Nguyen, FDA Orphan Products (ex officio)
- Jill Heemskerk, NINDS (ex officio)

 Spinal

uscular

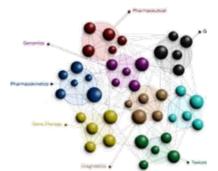


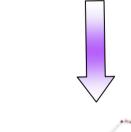


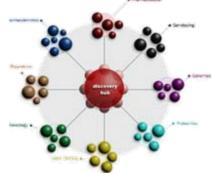
Lead Development Team

Chair: John McCall

- Chemistry
 - John McCall, PharMac, LLC
 - Graham Johnson, Rib-X
 - Weifan Zheng, UNC
- Biology
 - Keith Houck, EPA
 - Jill Heemskerk, NINDS
 - Sabina Robinson, SAIC



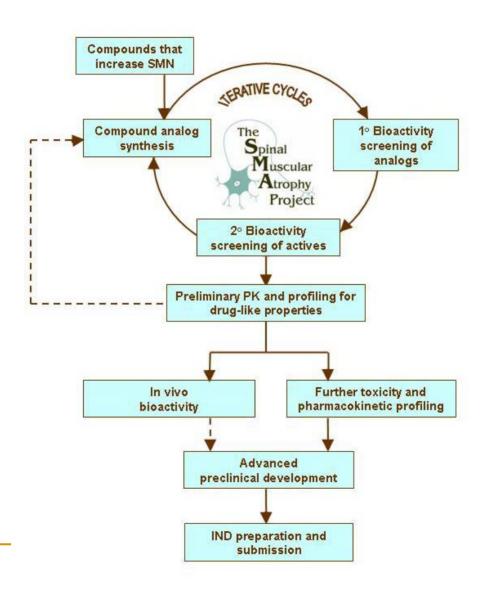




NEUROLOGICA



SMA Project Drug Discovery & Development Testing Funnel

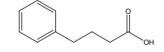


Starting Scaffolds

Indoprofen

- Increases SMN protein in vitro (Lunn et al, 2004)
- Improves in utero survival of SMA mice (Lunn et al 2004)

Phenylbutyrate:



- Increases SMN expression in vitro (Andreassi et al 2004)
- Extends survival of SMA mice (Burghes, unpublished)

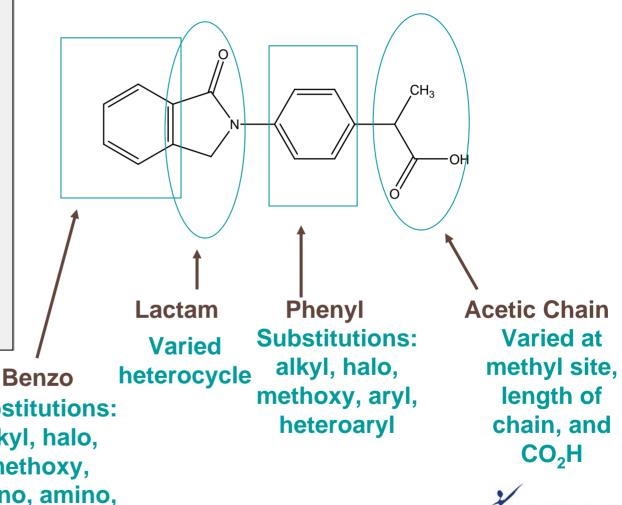




Indoprofen Structure Activity Strategy

SAR Goals

- Increase potency
- Eliminate toxicity
 - Cox Inhibition
- Improve BBB penetration



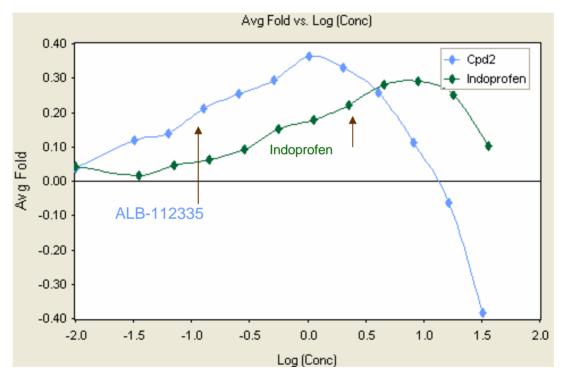


Substitutions: alkyl, halo, methoxy, cyano, amino, aryl, heteroaryl



Indoprofen SAR is Tractable

552 Analogs tested in Androphy splice reporter assay 145 Analogs with improved activity in reporter assay







Improved Brain Distribution

	Brain to Plasma Ratio
Indoprofen	0.03
Analog #1	0.4
Analog #2	15

Improvements to Indoprofen

- Increased potency 200 fold
- Increased efficacy 2.5 fold
- Enabled brain delivery
- Abolished Cox inhibitory structure

Systematic In Vivo Testing

- Pharmacologic studies
 - Formulation
 - Oral bioavailability
 - Brain distribution
 - Maximum tolerated dose
- SMA mouse model
 - Survival
 - Body weight
 - SMN expression studies

Getting to patients...

SMA Project studies

- Characterize drug-like properties
- Safety studies
- IND filing

Beyond the SMA Project

- Early phase clinical trials
- Industry licensing for full development

"Industry-style" not Industry

The SMA Project is a Collaborative Enabler

- Developing licensing opportunities (e.g., indoprofen analogs)
- IP-neutral enabling of outside efforts

Lessons Learned

- Steering committee expertise
 - Industry advisors
 - Fresh scientific perspective
- Industry-style operation
 - Flow plan with advancement criteria
 - Service organizations provide rapid turnaround
- Intensive project management
 - Tight, centralized coordination of projects
 - Internal expertise (Lead Development Team)

Applying the Pilot to Other Diseases

- Neurotherapeutics program coming in 2007
 - Medicinal Chemistry Service Facility
 - Central NIH Project Management
 - Flow Plan-driven projects
 - Resource leveraging

Acknowledgements

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- Gina Grossi

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- Brent Stockwell
- Arthur Burghes
- Glenn Morris
- Meg Winberg
- Cynthia Joyce
- Charlotte Sumner